Conclusions: The innate capacity to produce TNF-α and IL-10 upon LPS stimulation contributes to radiological progression of knee OA, even over a relative short follow-up period of two years. This finding suggests that innate production of TNF-α and IL-10 play a role in OA progression, which if confirmed implies that cytokines such as TNF-α could be pathophysiological targets for OA therapy.

A3

ONE YEAR FOLLOW-UP OF COLL 2-1, COLL 2-1 NO^2 AND MYELOPEROXYDASE SERUM LEVELS IN OSTEOARTHRITIC PATIENTS AFTER HIP OR KNEE REPLACEMENT

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Purpose: To determine Coll 2-1 level, a peptide of type II collagen triple helix, its nitrated form (Coll 2-1 NO_2) and myeloperoxydase (MPO) in serum of patients with knee or hip osteoarthritis (OA) before the surgery, three months and one year after knee or hip replacement.
Methods: Coll 2-1, Coll 2-1 NO_2 and MPO were measured by specific immunoassays in 83 asymptomatic aged subjects and in patients with knee (82) or hip (53) OA candidates for joint replacement. Sera were taken the day before surgery, three months and one year after hip or knee replacement. Coll 2-1 and Coll 2-1 NO_2 immunohistochemistry was performed on biopsies removed from cartilage lesions and surrounding area.
Results: Immunostainings with Coll 2-1 and Coll 2-1 NO_2 labelled extracellular matrix of fibrillated cartilage but not that of neighbouring area. Before surgery, Coll 2-1, Coll 2-1 NO_2 and MPO levels were higher in serum of OA patients than in asymptomatic aged subjects (Coll 2-1: $p<0.001$; Coll 2-1 NO_2: $p<0.001$ and MPO: $p<0.001$). Three months after joint replacement, Coll 2-1 and MPO serum levels were decreased ($p<0.001$) and even reached the control values for Coll 2-1. In contrast, Coll 2-1 NO_2 levels remained elevated. At one year follow-up, Coll 2-1 levels remained to the control values, MPO levels were similar to those measured at 3 months, and Coll 2-1 NO_2 levels were unchanged and comparable to the pre-surgery values. However, in patients with pre-surgery values above the median (more than 0.42 nM), Coll 2-1 NO_2 levels significantly and progressively decreased over one-year [at month 3 median: 0.56 nM (min: 0.14 nM-max: 4.05 nM; after one year median: 0.46 nM (min: 0.21 nM-3.66 nM] compared to the pre-surgery values [median: 0.72 nM (min: 0.43 nM-max: 4.21 nM)].
Conclusions: These findings suggest that Coll 2-1 is a relevant marker for the detection of late structural changes in OA patients. Furthermore, the normalization of Coll 2-1 levels three months after surgery indicates that Coll 2-1 is a disease-specific marker which is sensitive to the structural changes occurring in one single joint. Interestingly, MPO and Coll 2-1 NO_2 are increased in OA patients indicating that an oxidative stress occurs in the late stage of the disease.

A4

REARFOOT MOBILITY DETERMINES IF VALGUS WEDGED ORTHOSES REDUCE KNEE ADDUCTION MOMENTS IN MEDIAL KNEE OSTEOARTHRITIS (OA)

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Purpose: It has previously been demonstrated that patients with medial knee OA have increased loads across the medial knee, and we have shown that valgus posted foot orthoses have an effect on these knee adduction moments (AddM). This study aimed to determine whether the reductions in AddM in the presence of the wedge orthoses are related to frontal motion and position of the rearfoot in symptomatic medial compartment knee OA.
Methods: 40 subjects (63.4±9.9, mean±S.D, years of age, BMI of 28.5±4.4) with medial knee OA (symptomatic OA according to the *ACR Clinical Criteria for OA*, radiographic OA of Kellgren-Lawrence (K-L) grades 2-3, predominantly medial disease, and ambulatory knee pain ≥20mm on a 100mm VAS scale) were recruited from an ongoing double-blind randomized controlled trial [NLM Identifier: NCT00078453]. Exclusions included symptomatic arthritis of the hip, ankle, or foot; structural foot pathology; or any inflammatory arthritis. WOMAC site-specific surveys for each knee and weight-bearing AP lower extremity X-rays were obtained. Radiographic alignment of the rearfoot and lower leg along with anthropometric measurements were obtained by a blinded experienced clinician with the subject standing in two different stance-foot positions. Subjects were randomized into two groups, one consisting of treatment with custom molded foot orthosis posted to 7 degrees everted (valgus wedge) and the other with custom molded foot orthosis with no post (neutral). Kinematic and kinetic gait data were obtained as previously described using an optoelectronic system (Qualysis, Gothenburg, Sweden) and a multicomponent force plate (Bertec, Columbus, OH). The subjects wore the orthoses daily for three months and the gait tests were repeated. For statistical evaluation, subjects were dichotomized into "high mobility" with a rearfoot range of motion (ROM)>8° (12.4°±4.0) and "low mobility" ROM <8° (4.9°±3.1), and each treatment group was analyzed using ANOVA. Changes in the radiographic angles were compared between positions and groups and analyzed with Pearson's correlation coefficient and ANOVA.
Results: At 3 months, among the wedge-treated subjects there was a 12% reduction in knee AddM for those that were "high mobility," i.e., had greater frontal plane rearfoot motion, compared to those that were "low mobility" ($p=0.001$); in contrast, the neutral control group had no change in AddM regardless of frontal plane motion. In addition, the "low mobility" group did not have significant reductions in AddM, even when treated with the wedge. No correlation was demonstrated between the reduction in moments and either WOMAC pain severity or radiographic severity as determined by K-L grade. The changes in the radiographic alignment demonstrated that a wider stance position resulted in less varus of the rearfoot and lower leg and confirmed the dichotomization of the groups with a strong correlation between changes in radiographic alignment and anthropometric measurements ($R^2=0.69$ $p<0.001$). The changes in lower extremity radiographic alignment were also correlated to the reduction of knee

A3 – Table 1. Serum levels [median (range)] of Coll 2-1, Coll 2-1 NO_2 and MPO in asymptomatic subjects and OA patients.

	Asymptomatic subjects	OA subjects		
		Before surgery	3 months after joint replacement	1 year after joint replacement
COLL 2-1 (nM)	123.69 (37.60-284.09)	156.84 (45.77-460.80)	119.58 (17.00-250.19)	114.61 (24.38-303.82)
COLL 2-1 NO2 (nM)	0.26 (<0.03-1.66)	0.42 (0.10-4.21)	0.45 (<0.03-4.05)	0.42 (0.21-3.66)
MPO (ng/ml)	67.00 (0.00-212.00)	153.73 (0.00-1213.00)	92.00 (0.00-859.00)	98.70 (39.90-789.60)

adduction moments when the subjects wore wedged orthotics (R^2=0.66 $p<0.001$).

Conclusions: These data suggest that patients with greater frontal plane rearfoot motion may have a greater response to treatments with valgus posted foot orthoses compared to those with restricted frontal plane motion. This is consistent with the theory that motion at the leg segments distal to the knee may have substantial effect on the forces within the knee, and suggests that evaluation of rearfoot motion and position may permit identification of patients likely to benefit from such unloading therapy.

A5

OSTEOPHYTES IN MURINE EXPERIMENTAL OSTEOARTHRITIS RESEMBLE TGF-BETA INDUCED OSTEOPHYTES. THE ROLE FOR BMP IN EARLY OSTEOARTHRITIC OSTEOPHYTE FORMATION APPEARS TO BE LIMITED

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Purpose: A typical feature of osteoarthritis (OA) is osteophyte formation. They cause joint deformaties, pain and movement restriction in patients with OA. Both Transforming Growth Factor-beta (TGF-beta) and Bone Morphogenetic Protein2 (BMP-2) are able to induce osteophytes when injected intra-articularly into murine knee joints. This study is focused on the involvement of TGF-beta and BMP2 in early osteophyte formation in experimental OA. We compared TGF-beta1 with BMP-2-induced osteophytes and investigated the role for BMPs in early osteophyte development in OA by blocking BMPs with Gremlin.

Methods: Knee joints of C57Bl/6 mice were injected i.a. with adenoviruses overexpressing either TGF-beta1 (ad-TGF-beta) or BMP-2 (ad-BMP2). In addition, we injected C57Bl/6 knee joints with collagenase to induce instability-induced OA. Knee joints were isolated at various time points for histological assessment of osteophytes. To investigate whether BMPs contribute to TGFbeta-induced osteophyte formation ad-TGF-beta was co-injected with an adenovirus overexpressing the BMP inhibitor Gremlin (ad-Gremlin) In addition, we used Gremlin overexpression to investigate the role of BMPs in early osteophyte formation in an instability-induced OA (collagenase-induced) model. Knee joints were isolated 7 days after injection of ad-TGF-beta or collagenase injection for histology.

Results: Upon adenoviral overexpression of BMP2 we observed osteophyte formation. By day 3 we observed chondrogenic outgrowth of the growth plates where the growth plate meets the joint space on the femur and on the tibia. After 7 days chondrogenesis was observed on the patella and in the collateral ligaments. By day 21 most osteophytes had cores of bone and cruciate ligaments showed chondrogenesis.

TGF-beta injection showed a different pattern. Osteophyte formation started in the periosteum located at the bone adjacent to the femoral-tibial jointspace. Chondrogenesis was also observed at the attachement site of the collateral ligaments. In some joints there was also chondrogenesis on the patella. In time (gradually), these osteophytes turned into bone. However, they remained much smaller than BMP2-induced osteophytes, even at later time points up to 3 months. The patterns of osteophyte location and osteophyte appearance of TGF-beta-induced and in the instability-induced OA model showed a high resemblance, especially at early time points. This suggests that the osteophytes in OA might initially be more TGF-beta driven than BMP-driven. To evaluate the role of BMPs in early osteophyte formation we inhibited BMPs with Gremlin. Ad-Gremlin totally blocked BMP2-induced osteophyte formation, indicating that gremlin potently inhibited BMP activity. However, when ad-Gremlin was co-injected with ad-TGF-beta, osteophyte formation continued and no differences were observed when compared to ad-TGF-beta alone. Moreover, when BMPs were blocked in the instability-induced OA model no block of osteophyte formation was observed.

Conclusions: Both BMP2 and TGF-beta were able to induce osteophytes in murine knee joints, but the locations of the osteophytes was different, very likely due to stimulation of different cell types. BMP2-induced osteophytes were blocked by gremlin, but TGF-beta-induced osteophyte formation continued as well as the osteophyte formation in a murine OA-model. These data suggest that BMPs have a limited role in early osteophyte formation in OA. The role of BMP in maturing osteophytes might still be important and remains to be investigated.

A6

A PROSPECTIVE RANDOMIZED CLINICAL STUDY OF AUTOLOGOUS OSTEOCHONDRAL TRANSPLANTATION VERSUS MICROFRACTURE FOR THE TREATMENT OF OSTEOCHONDRAL DEFECTS IN THE KNEE JOINT IN YOUNG ATHLETES. A 5 YEAR FOLLOW-UP

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Purpose: The purpose of this study was to compare the outcomes of mosaic type autologous osteochondral transplantation (OAT) and microfracture (MF) procedures for the treatment of the articular cartilage defects of the knee joint in young active athletes.

Methods: Between the 1998 and 2002, a total of 60 athletes with a mean age of 24.3 years (15 to 40) and with a symptomatic lesion of the articular cartilage in the knee were randomized to undergo either autologous osteochondral transplantation or microfracture procedure. Only those athletes playing in competitive sports were included in the study. There were 28 athletes in OAT group and 29 athletes in MF group. The mean duration of symptoms was 21.32 $\pm$5.57 months and the mean follow-up was 5 years (range from 4 to 7 years) and none of the athletes had prior surgical interventions to the affected knee. Patients were evaluated using a modified Hospital for Special Surgery (HSS) and International Cartilage Repair Society (ICRS) scores, x-rays, MRI and clinical assessment. An independent observer performed a follow-up examination after six month, and every year after surgery. Postoperatively, arthroscopy with biopsy for histological evaluation was carried out. A radiologist and a pathologist, both of whom were blinded to each patient's treatment, did the radiological and histological evaluations.

Results: After 5 years, only OAT group maintained significant clinical improvement ($p<0.05$). Although, both groups HSS and ICRS scores declined, only MF group showed significant deterioration over the 5 years follow-up. According to the modified HSS and ICRS scores, functional and objective assessment showed that 92% maintained excellent or good results after OAT compared with 43% after MF procedure ($p<0.001$). In 1, 2, 3, 4 and 5 years after the operations the HSS and ICRS showed statistically significantly better results in the OAT group (p=0.03; p=0.006; p=0.006; p=0.05; p=0.05). Younger athletes did better in both groups. There was one failure in the OAT-group, and twelve in the MF-group. Macroscopic evaluations during arthroscopy 23.5 months after the operations were performed for 16-OAT and 22-MF group's patients. The ICRS Cartilage Repair Assessment for macroscopic evaluation demonstrated excellent or good repairs in 84% after OAT and in 57% after microfracture. Biopsy specimens were obtained from 58% of the patients, and histological evaluation of repair showed better scores (according to ICRS) for